REMARKS

Status Summary

Claims 1, 5, 7, 9-26, 28, 29, and 31-78 are pending in the present application. Claims 1, 5, 7, 9-26, 28, 29, and 31-78 presently stand rejected.

Claims 1, 5, 7, 9-26, 28, 29, 31, 32, and 56-78 have been rejected by the United States Patent and Trademark Office (hereinafter "the Patent Office") under 35 U.S.C. § 112, first paragraph, upon the contention that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors had possession of the claimed invention at the time the application was filed. More particularly, the Patent Office contends that the phrase "a heterologous promoter which is not related to a promoter from a retrovirus upon which the retroviral vector is based" defines a genus of promoters that is not supported by the specification as filed.

Claims 1, 5, 7, 9-26, 28, 29, 31, 32, and 56-78 have been rejected by the Patent Office under 35 U.S.C. § 112, second paragraph, upon the contention that the phrase "a heterologous promoter which is not related to a promoter from a retrovirus upon which the retroviral vector is based" is indefinite.

Claims 1, 5, 7, 9-26, 28, 29, and 31-78 have been rejected under 35 U.S.C. § 103(a) on several bases over various combinations of Couture *et al.*, 1994 (5 *Human Gene Therapy* 667-677; hereinafter "Couture); Faustinella *et al.*, 1994 (5 *Human Gene Therapy* 307-312; hereinafter "Faustinella"); Mee & Brown, 1990 (88 *Gene* 289-292; hereinafter "Mee"); Mehigh *et al.*, 1993 (71 *J Anim Sci* 687-693; hereinafter "Mehigh"); Miller *et al.*, 1989 (7 *Biotechniques* 980-990; hereinafter "Miller"); Panganiban & Temin, 1984 (81 *PNAS* 7885-7889; hereinafter "Panganiban"); Price *et al.*, 1987 (84 *PNAS* 156-160; hereinafter "Price"); Longmore *et al.*, 1993 (82 *Blood* 2386-2395; hereinafter "Longmore"); and Kay *et al.*, 1993 (262 *Science* 117-119; hereinafter "Kay").

Claims 1, 5, 7, 17, 28, 33, 43, 51, 56, 66, and 74 have been amended. Support for the amendments can be found throughout the specification as filed, including particularly at page 10, second paragraph, of WO 96/97748 (the PCT International

Patent Application Publication of PCT/EP95/03445, the PCT Application upon which the instant application is based). Additional support can be found on in the claims as filed, including particularly Claim 22.

No new matter has been added by any of the amendments to the claims. Reconsideration of the application as amended and based on the remarks set forth herein below is respectfully requested.

Claim Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1, 5, 7, 9-26, 28, 29, 31, 32, and 56-78 have been rejected by the United States Patent and Trademark Office (hereinafter "the Patent Office") under 35 U.S.C. § 112, first paragraph, upon the contention that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that the inventors had possession of the claimed invention at the time the application was filed. More particularly, the Patent Office contends that the phrase "a heterologous promoter which is not related to a promoter from a retrovirus upon which the retroviral vector is based" defines a genus of promoters that is not supported by the specification as filed. After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that the phrase "a heterologous promoter which is not related to a promoter from a retrovirus upon which the retroviral vector is based" is adequately supported by the specification as filed. In particular, applicants respectfully submit that the specification as filed discloses that the heterologous promoter can be "any promoter, including those directing tissue specific expression". *See* WO 96/07748, page 9.

Furthermore, applicants respectfully submit that one of the main concerns in the area of retroviral gene therapy addressed by the claimed vectors relates to intracellular recombination between retroviral sequences to produce potentially pathogenic replication competent virus. *See* page 3 of PCT International Patent Application Publication WO 96/07748 (hereinafter "WO 96/07748), the publication of the PCT

Application upon which the instant U.S. patent application is based. Thus, the use of "heterologous promoters that are not related to a promoter from a retrovirus upon which the retroviral vector is based" is designed to minimize the sequence homology between the inserted heterologous promoter and other sequences present on the retroviral vector (*e.g.* sequences present in the 5' LTR). As stated on page 10 of PCT WO 96/07748, "[p]romoter conversion (ProCon) vectors do not resemble retroviruses because they no longer carry U3 retroviral promoters after conversion thus reducing the possibility of genetic recombination". As such, applicants respectfully submit that the phrase "a heterologous promoter which is not related to a promoter from a retrovirus upon which the retroviral vector is based" is adequately supported by the specification as filed, and respectfully request that the instant rejection be withdrawn.

However, in an effort to facilitate prosecution of the instant claims, applicants have amended claims 1, 17, and 28 to recite "a heterologous promoter". Additionally, claims 33, 43, and 51 recite "a promoter from a cellular gene" and claims 56, 66, and 74 recite "a heterologous retroviral promoter". Applicants respectfully submit that the Patent Office concedes that the specification as filed discusses heterologous promoters, including the MMTV promoter and the Whey Acidic Protein promoter. Additional heterologous promoters that are disclosed in the application as filed include β-lactoglobulin and casein-specific promoters, pancreas-specific promoters including the carbonic anhydrase II and β-glucokinase promoters, lymphocyte-specific promoters including immunoglobulin and MMTV lymphocyte-specific regulatory elements, and MMTV promoters conferring responsiveness to glucocorticoid hormones or directing expression to the mammary glands (*see* WO 96/07748 at page 6). As such, applicants respectfully submit that there is adequate written description for the genus "heterologous promoters", including the sub-genera "a promoter from a cellular gene" and "a heterologous retroviral promoter", as presently recited in the claims.

Furthermore, applicants respectfully submit that in determining whether the application includes an adequate written description of the claims, the specification as filed is supplemented by the knowledge of the skilled artisan at the time of filing, and

thus includes a much greater scope of "heterologous promoters" than is explicitly disclosed. According to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶1, "Written Description" Requirement (hereinafter the "Guidelines"), "a patent specification 'need not teach, and preferably omits, what is well known in the art'." Guidelines, 66 Federal Register at page 1103 (emphasis added; citing Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534 (Fed. Cir. 1987)). Thus, applicants respectfully submit that the list of heterologous promoters explicitly recited in the specification is exemplary only, and that many additional heterologous promoters were known to one of ordinary skill in the art at the time the instant application was filed.

Summarily, applicants respectfully submit that that at the time of filing, one of ordinary skill in the art would understand that the inventors were in possession, *inter alia*, of a retroviral vector characterized by a deletion of all or part of the U3 region of the 3' LTR into which a cloning site was introduced so that any promoter of interest could be cloned. Applicants further respectfully submit that the Patent Office's contention that "applicants have failed to [give] a description of the claimed genus of promoters in the instant specification at the time of filing" is unsupported by any scientific reasoning, as the specification as filed clearly states that the polylinker allows for the easy insertion of any promoter (*see* WO 96/07748 at page 9). Thus, applicants respectfully submit that one of ordinary skill in the art would have understood that any promoter could be cloned into the vector, and as such, the Patent Office has not overcome the strong presumption that there is an adequate written description of the claimed invention in the application as filed. *See* Guidelines, 66 Federal Register at page 1100 (emphasis added).

Applicants respectfully submit that as a result of the amendments to claims 1, 17, 28, 56, 66, and 74, the rejection of these claims under 35 U.S.C. § 112, first paragraph, has been addressed. Furthermore, claims 5, 7, 9-16, 18-26, 29, 31, 32, 57-65, 67-73, and 75-78 all depend directly or indirectly from amended claims 1, 17, 28, 56, 66, and 74, and thus the rejection of these claims is also believed to have been addressed. Accordingly, applicants respectfully request that the rejection of claims 1,

5, 7, 9-26, 28, 29, 31, 32, and 56-78 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1, 5, 7, 9-26, 28, 29, 31, 32, and 56-78 have been rejected by the Patent Office under 35 U.S.C. § 112, second paragraph, upon the contention that the phrase "a heterologous promoter which is not related to a promoter from a retrovirus upon which the retroviral vector is based" is indefinite. According to the Patent Office, the metes and bounds of the claimed promoter are unclear. Claims 5 and 16 have also been rejected under this section upon the contention that there is insufficient antecedent basis for the phrase "said heterologous vector" in claim 5. After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

Turning first to the rejection of claims 5 and 16, applicants have amended claim 5 to recite "said retroviral vector", for which applicants respectfully submit there is antecedent basis in claim 5. Thus, applicants respectfully submit that the rejection of claims 5 and 16 under this section has been addressed, and respectfully request the withdrawal of the rejection.

Continuing with the rejections under 35 U.S.C. § 112, second paragraph, applicants respectfully submit that the objected to phrase has been amended in all relevant claims (*i.e.* claims 1, 17, 28, 56, 66, and 74). Further, claims 1, 17, 28, 56, 66, and 74 recite "a heterologous promoter", "a promoter from a cellular gene", or "a heterologous retroviral promoter". According to the specification as filed, a "heterologous" promoter is a promoter that is linked to DNA sequences with which it is not normally found in nature (*see* WO 96/07748 at page 9). Applicants further respectfully submit that this use of the term "heterologous" is consistent with the understanding of the skilled artisan, *i.e.*, that the promoter is one not normally found linked to the sequences to which is it linked in the claimed vectors. Applicants further submit that this meaning is also consistent with the phrase "a heterologous promoter which is not related to a promoter from a retrovirus upon which the retroviral vector is

based". Thus the instant amendments are solely intended for clarity and to aid in the prosecution of the claims, and are not to be construed as a surrender of any subject matter.

Applicants respectfully submit that as a result of the amendments to claims 1, 17, 28, 56, 66, and 74, the rejection of these claims under 35 U.S.C. § 112, second paragraph, has been addressed. Furthermore, claims 5, 7, 9-16, 18-26, 29, 31, 32, 57-65, 67-73, and 75-78 all depend directly or indirectly from amended claims 1, 17, 28, 56, 66, and 74, and thus the rejection of these claims is also believed to have been addressed. Applicants respectfully request that the rejection of claims 1, 5, 7, 9-26, 28, 29, 31, 32, and 56-78 under 35 U.S.C. § 112, second paragraph, be withdrawn at this time.

Claim Rejections under 35 U.S.C. § 103(a)

All of the pending claims have been rejected under 35 U.S.C. § 103(a) over Couture in view of Faustinella, and in addition over these references combined with various combinations of Mee, Mehigh, Miller, Panganiban, Price, Longmore, and Kay. These rejections and the claims to which they have been applied are summarized as follows:

Rejection No.	Claims Rejected	References Cited
1	1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78	Couture in view of Faustinella
2	1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78	Couture in view of Faustinella, and further in view of Mee
3	1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-36, 38, 39, 42-49, and 51-55	Couture in view of Faustinella, and further in view of Mehigh

4	1, 13, 14, 33, 40, 41, 56, 63, and 64	Couture in view of Faustinella; or Couture in view of Faustinella, and further in view of Mee; or Couture in view of Faustinella, and further in view of Mehigh; and further as evidenced by Miller and Panganiban
5	1, 10, 33, 37, 56, and 60	Couture in view of Faustinella; or Couture in view of Faustinella, and further in view of Mee; or Couture in view of Faustinella, and further in view of Mehigh; and further as evidenced by Price
6	17, 20, 21, 26, 28, 43, 50-53, 66, and 73-76	Couture in view of Faustinella; or Couture in view of Faustinella, and further in view of Mee; or Couture in view of Faustinella, and further in view of Mehigh; and further as evidenced by Longmore and Kay

Obviousness Rejection No. 1

Claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 have been rejected as obvious over Couture in view of Faustinella. According to the Patent Office, Couture discloses retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses. Also, Couture's vectors comprise a CAT gene and a neo gene. Couture is also asserted to teach that after packaging, the U3 region appears at the 5' LTR and serves as a promoter for all genes in the body of the vector. The Patent Office concedes, however, that Couture does not disclose the use of a multiple cloning site in the U3 region.

The Patent Office contends, however, that this deficiency is cured by Faustinella, which is asserted to teach a MoMLV-based vector comprising a partial deletion of the 3' U3 region, into which a polylinker has been inserted. From these assertions, the Patent Office alleges that it would have been obvious to one of ordinary

skill in the art at the time the instant application was filed to modify the vectors of Couture by adding a multiple cloning site of Faustinella because Faustinella shows that multiple cloning sites may be used to insert sequences of interest into a U3 region of a retroviral vector. After careful consideration of the instant rejection and the Patent Office's asserted basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Applicants respectfully submit that the Patent Office has not established a *prima facie* case of obviousness over these two references for several reasons including, *inter alia*, that it is only by using impermissible hindsight reconstruction that the two cited references can be combined in an attempt to arrive at the claimed invention. Additionally, applicants submit that even if the two references are combined, the references must be considered in their entireties, and when this is done, it is clear that the combination of Couture and Faustinella does not teach or suggest the claimed invention.

Initially, applicants respectfully submit that the Patent Office has not presented a *prima facie* case of obviousness over the cited references based on the assertion that it would have been obvious to a person of ordinary skill in the art to modify the vectors of Couture by adding a multiple cloning site of Faustinella because Faustinella shows that multiple cloning sites may be used to insert sequences of choice in a U3 region of a retroviral vector. Even assuming *arguendo* that the Patent Office's contentions regarding Faustinella are correct, the cited references cannot be combined as the Patent Office asserts to arrive at the claimed invention because adding a polylinker to Couture's vector does not create a retroviral vector with a partially deleted U3 region.

Independent claim 1 of the instant application is representative of the subject matter that has been rejected under the instant rejection. Claim 1 recites, *inter alia*, the following: a retroviral vector comprising in 5' to 3' order (a) a 5' long terminal repeat region of the structure U3-R-U5; (b) one or more coding sequences, said sequences being inserted into the body of the vector; and (c) a 3' long terminal repeat region comprising a partially deleted U3 region into which has been inserted a polylinker

sequence containing a heterologous promoter, wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous promoter and said heterologous promoter regulating expression of said one or more coding sequences in said target cell. Independent claims 17, 28, 56, 66, and 74 recite similar or identical elements. These independent claims also recite that the promoter cloned into the polylinker sequence regulates the expression of the one or more coding sequences after infection of a target cell. As such, elements of these claims include *inter alia* (a) a 3' LTR that is characterized by a U3 deletion (*i.e.* is an incomplete LTR); (b) a polylinker; and (c) a heterologous promoter that directs the expression of a coding sequence of interest present within the body of the vector only after promoter conversion.

Applicants respectfully submit that Couture teaches a retroviral vector that contains a complete, although chimeric, U3 region. Couture explicitly states on page 669 that they built chimeric LTRs "based on the substitution of the MoMLV U3 region with the U3 region from the murine retroviral isolates SL3-3, AKV, Xeno, HaMSV, and MPSV" (emphasis added). This was accomplished by employing conserved restriction sites present in the 3' LTRs of these retroviruses. As such, the vectors disclosed by Couture were specifically designed to have complete U3 regions, and thus cannot be deemed to motivate one of ordinary skill in the art to produce a retroviral vector with a partially deleted U3 region as claimed in the instant application.

Additionally, it cannot be said that the vectors of Couture have a deletion of the U3 region. The only compositions disclosed in Couture that actually had U3 deletions were intermediates used in the preparation of the vectors; the vectors themselves (*i.e.* the vectors that Couture considered useful) intentionally corrected the U3 deletion by insertion of the missing U3 sequences from a related retrovirus.

In fact, when Couture is taken as a whole and in context, one of ordinary skill in the art would not have been motivated to produce vectors that had 3' U3 deletions at all since the retroviral vectors disclosed therein were designed to test the abilities of

sequences present in the 3' U3 regions of the various retroviral LTRs to affect the tropism and expression levels of vector-encoded genes, and to do this the U3 deletion present in the intermediates were repaired. Stated another way, the vectors of Couture are designed to have complete chimeric LTRs in order to take advantage of the abilities of different retroviral LTRs to direct the expression of operatively linked genes in different tissues. As the sequence elements that are responsible for the different tissue tropisms seen for different retroviruses are found within the 3' U3 regions of the retroviruses, one of ordinary skill in the art would not have considered constructing retroviral vectors with deletions of the 3' U3 region because these deletions would be expected to remove the sequences that are critical to the functioning of Couture's vectors. Thus, Couture teaches away from constructing retroviral vectors with 3' U3 deletions.

Turning now to the Faustinella reference, applicants respectfully submit that the Patent Office has indicated throughout the prosecution of the instant application that this reference is only being relied upon to provide the use of a polylinker as a cloning site. Applicants respectfully submit, however, that the Patent Office has not shown why one of ordinary skill in the art would have read Couture and been motivated to add a polylinker at all, since Couture clearly based the disclosed vectors on replacement of one region of U3 with that of a highly related retrovirus using restriction sites that were common to the various retroviruses or already present in convenient locations. In essence, the Patent Office has combined Faustinella with Couture to address a problem that was neither encountered nor suggested by Couture. Thus, there is no motivation to combine the cited references because the element the Patent Office asserts is supplied by Faustinella is one that one of ordinary skill in the art would not have been motivated to include in Couture's vectors.

Therefore, applicants respectfully submit that the combination of the cited references does not suggest the desirability of making the modification. Thus, it is respectfully submitted that no motivation to combine the references can be found and a *prima facie* case of obviousness has not been established.

Applicants further respectfully submit that Faustinella's disclosure is limited in that the purpose of the 3' U3 deletion was to create a self-inactivating vector by deletion of the promoter/enhancer sequences present within the 3' LTR. Applicants respectfully submit that the vectors of the instant application are not self-inactivating. Thus, when taken in its entirety, Faustinella teaches away from deleting U3 sequences and then introducing a promoter into the deletion because to do so would destroy the self-inactivation character of the vector that the U3 deletion was designed to create.

It is clear from a close reading of Faustinella that if the 3' LTR polylinker is to be used as a cloning site for a promoter, that promoter must be operatively linked to a gene of interest, because only when the inserted promoter is operatively linked to a gene of interest is a self-inactivating vector produced. This promoter-gene of interest pair is in fact what is disclosed in Faustinella: the polylinker present in the 3' U3 region is used only for the insertion of a luciferase gene operatively linked to an RSV promoter or a hygromycin-resistance gene operatively linked to a TK promoter. The cloning of a promoter/coding sequence pair does not destroy the self-inactivation function of the Faustinella vectors because transcription from the promoters through the operatively linked genes would terminate that the 3' end of the linked gene and would thus not be expected to cause insertional activation of host genes. Since the only reason a 3' U3 deletion is present in the Faustinella vector is to remove the 3' U3 promoter sequences to create a self-inactivating vector, applicants respectfully submit that Faustinella teaches away from inserting a promoter and/or regulatory sequences only into the polylinker inserted into the 3' LTR.

Applicants respectfully submit that insertion of a competent promoter into the polylinker site of pS3 without operatively linking the promoter to a coding sequence would destroy the self-inactivation feature that the 3' LTR deletion was solely designed to produce. Consequently, Faustinella when read as a whole does not suggest the insertion of a promoter only into the polylinker present within the 3' U3 deletion because to do so would destroy the principle of operation of the Faustinella vector that the deletion was intended to create in the first place. As such, applicants respectfully submit that Faustinella, alone or in combination with Couture, cannot be read to

suggest a vector with a 3' U3 deletion into which a competent promoter and/or regulatory sequences alone are inserted.

Thus, the teachings of Faustinella are believed to be overstated in the assertion that this reference shows that multiple cloning sites may be used to insert "sequences of choice" into a partially deleted U3 region of a retroviral vector. On the contrary, applicants respectfully submit that Faustinella can only be interpreted to teach that if a promoter is cloned into the 3' U3 deletion, a coding sequence must be operatively linked to the promoter in order to retain the benefit of the 3' U3 deletion (*i.e.* the self-inactivation function).

This is in contrast to the vectors of the instant invention, which have a cloning site located in the 3' LTR into which promoters and/or other transcriptional regulatory elements only are inserted. These vectors are not designed to be self-inactivating vectors (*see* WO 96/07748, pages 4-5), and require passage through the retroviral lifecycle in order to have the promoter and coding sequence of interest become operatively linked. Accordingly, applicants respectfully submit that Faustinella cannot be read as suggesting the 3' U3 deletion that is missing from the Couture vectors, and thus there is no motivation to combine the cited references as suggested by the Patent Office to arrive at the claimed vectors.

Furthermore, applicants respectfully submit that one of ordinary skill in the art would not have looked to combine Couture with Faustinella because this would have changed the principle of operation of not only the Faustinella reference (as discussed in more detail hereinabove), but of the Couture reference as well. As is clearly stated in the Manual of Patent Examining Procedure at § 2143.01, "if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious". Since Couture discloses the use of chimeric LTRs to influence tissue tropism and gene expression, the proposed modification of Couture's vectors with the asserted teachings of Faustinella (*i.e.* the deletion of some U3 sequences and/or the insertion of a polylinker) would render the vectors unsatisfactory for their intended purposes by removing the sequences by

which this tissue tropism and gene expression are regulated. Thus, according to M.P.E.P. § 2143.01, no suggestion or motivation to combine the references to make the proposed modification can be seen.

Summarily, with respect to the instant rejection under § 103(a) over Couture in view of Faustinella, applicants respectfully submit that the cited combination does not suffice to create a *prima facie* case of obviousness for several reasons. First, there is no motivation to combine the cited references. Second, only by using impermissible hindsight vision can the references be combined at all. Third, the art at the time of filing of the instant application gave no reasonable expectation that the cited combination could be combined with a reasonable expectation of success in creating the instantly claimed subject matter. And finally, even if the references are combined as suggested by the Patent Office, the combination does not disclose each and every element of the presently claimed subject matter.

Accordingly, applicants respectfully submit that the rejection of claims 1, 5, 9, 11, 12, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 62, 65-72, and 74-78 over Couture in view of Faustinella is improper, and respectfully request that the rejection be withdrawn. Allowance of these claims is also respectfully requested.

Obviousness Rejection No. 2

Claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78 have been rejected as obvious over the combination of Couture and Faustinella as applied in the above-discussed Obviousness Rejection No. 1, and further in view of Mee. The Patent Office bases this rejection on those contentions made in reference to the Couture and Faustinella references in combination with the asserted disclosure in Mee of a retroviral vector comprising an MMTV LTR. From this combination, the Patent Office contends that it would have been obvious to modify the vector of Couture in view of Faustinella by insertion of an MMTV promoter region in a deleted 3' U3 region of a retroviral vector because Mee shows that their LTR promoter may be used to manipulate gene expression in a variety of cell types. After careful consideration of the instant rejection and the Patent Office's asserted basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that the addition of the Mee reference does not cure the deficiencies of the combination of Couture and Faustinella outlined above, which are incorporated herein by reference. To reiterate, Couture and Faustinella fail to suggest a retroviral vector characterized by an incomplete 3' U3 region and a heterologous promoter that upon promoter conversion becomes operatively linked to a gene of interest encoded within the body of the vector.

This deficiency is not cured by the addition of the Mee reference. As clearly stated on page 290 of Mee, the vectors were designed such that the gene of interest was cloned "such that a start codon in the inserted sequence will be the first AUG downstream of the *tsp* of the MMTV *HRE* promoter". Thus, Mee discloses a plasmid vector wherein the MMTV promoter element is operatively linked to the gene it is to regulate from the outset. Other genes that are disclosed in Mee, including the *aph* gene and the *cat* gene, were also cloned so that they were operatively linked to their promoters. Thus, even assuming *arguendo* that Mee discloses the use of an MMTV LTR for the manipulation of gene expression in a variety of cell types, applicants respectfully submit that it does not provide the missing suggestion of Couture and Faustinella of a retroviral vector characterized by an incomplete 3' U3 region and a heterologous promoter that upon promoter conversion becomes operatively linked to a gene of interest to which it was not operatively linked prior to the promoter conversion event. Thus, applicants respectfully submit that similar to the reasons presented hereinabove with regard to the previous obviousness rejection, a *prima facie* case of obviousness has not been presented with regard to the instant combination of references, and further that even if the references were combined as suggested by the Patent Office, the combination does not arrive at the instantly claimed invention.

Accordingly, applicants respectfully submit that the rejection of claims 1, 5, 7, 9, 11, 12, 16-25, 28, 29, 31, 32, 56-59, 61, 62, 65-72, and 74-78 over the combination of Couture and Faustinella as applied in Obviousness Rejection No. 1, and further in view of Mee is improper, and respectfully request that Obviousness Rejection No. 2 be withdrawn. Allowance of these claims is also respectfully requested.

Obviousness Rejection No. 3

Claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-36, 38, 39, 42-49, and 51-55 have been rejected over the combination of Couture and Faustinella as applied in the above-discussed Obviousness Rejection No. 1, and further in view of Mehigh. The Patent Office bases this rejection on the contentions made in reference to the Couture and Faustinella references, in combination with the asserted disclosure in Mehigh of a retroviral vector comprising a WAP promoter. From this combination, the Patent Office contends that it would have been obvious to modify the vector of Couture in view of Faustinella by insertion of a WAP promoter region in a deleted 3' U3 region of a retroviral vector because Mehigh shows that such vectors are inducibly expressed and may allow for increased milk production in cattle. After careful consideration of the instant rejection and the Patent Office's asserted basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

The discussions presented hereinabove with regard to the deficiencies of the Couture and Faustinella references are incorporated herein. Applicants respectfully submit that Mehigh does not cure these deficiencies because Mehigh does not teach or suggest the construction of a vector that undergoes promoter conversion to operatively link the disclosed promoters to the genes of interest. As is clearly stated in the Abstract, "the gene encoding synthetic bGRF... was fused to the whey acidic protein promoter (WAP) or the mouse mammary tumor virus promoter (MMTV)". Consequently, it is clear from the disclosure that at best Mehigh teaches the use of the WAP and MMTV promoters to control the expression of linked genes.

Thus, Mehigh does not cure the deficiencies of Couture in combination with Faustinella, because Mehigh does not provide the missing suggestion of Couture and Faustinella of a retroviral vector characterized by an incomplete 3' U3 region and a heterologous promoter that upon promoter conversion becomes operatively linked to a gene of interest to which it was not operatively linked prior to the promoter conversion event. Thus, Mehigh in combination with Couture and Faustinella does not support a *prima facie* case of obviousness.

Furthermore, with regard to claims 38 and 39 specifically, these claims recite that the body of the retroviral vector includes coding sequences that are selected from the group consisting of marker genes, therapeutic genes, antiviral genes, antitumor genes, cytokine genes and combinations thereof (claim 38) including, but not limited to a β-galactosidase gene, a neomycin gene, a Herpes Simplex Virus thymidine kinase gene, a puromycin gene, a cytosine deaminase gene, a hygromycin gene, a secreted alkaline phosphatase gene, a guaninephosphoribosyl transferase (gpt) gene, an alcohol dehydrogenase gene, and a hypoxanthine phosphoribosyl transferase (HPRT) gene (claim 39). Applicants respectfully submit that the cited references do not disclose or suggest a retroviral vector that is characterized by a partially deleted U3 region into which a promoter from a cellular gene is inserted that regulates expression of any of these coding sequences after infection of a target cell as recited in claims 38 and 39. Thus, particularly with regard to these claims, applicants respectfully submit that a *prima facie* case of obviousness has not been presented.

Accordingly, applicants respectfully request that the obviousness rejection of claims 1, 5, 7, 9, 11, 12, 15-25, 28, 29, 31-36, 38, 39, 42-49, and 51-55 over Couture and Faustinella as applied in Obviousness Rejection No. 1, and further in view of Mehigh be withdrawn. Allowance of these claims is also respectfully requested.

Obviousness Rejection No. 4

Claims 1, 13, 14, 33, 40, 41, 56, 63, and 64 have been rejected over the combinations recited in the above-discussed Obviousness Rejection Nos. 1-3, and further as evidenced by Miller and Panganiban. In addition to the assertions made with respect to the previously discussed obviousness rejections, the Patent Office asserts that Miller and Panganiban disclose retroviral vectors with deletions of the *gag*, *pol*, and *env* genes (Miller) and that the 3' end of the *pol* gene encodes the *int* locus, which is required for integration of the reverse transcribed retroviral genome to form a provirus. After careful consideration of the instant rejection and the Patent Office's asserted basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Applicants respectfully submit that even assuming *arguendo* that the Patent Office's characterization of the Miller and Panganiban references is correct, these references do not cure the deficiencies discussed hereinabove for the combination of Couture and Faustinella. Applicants respectfully submit that Couture and Faustinella are asserted to suggest a retroviral vector having an incomplete 3' U3 and a polylinker into which a heterologous promoter is inserted that upon promoter conversion becomes operatively linked to a gene encoded within the body of the vector. As discussed in greater detail hereinabove, these references do not in fact suggest a vector of this particular design. Miller and Panganiban do not cure this deficiency. Indeed, the disclosures of Miller and Panganiban are limited to vectors containing modifications of retroviral protein genes or packaging signals (Miller) and/or the identification of the location of the *int* locus. The vectors do not include 3' U3 deletions, heterologous promoters, or polylinkers located within the 3' LTR. Thus, Miller and Panganiban do not cure the deficiencies of Couture and Faustinella, and as such, the recited combination cannot be deemed to suggest the presently claimed subject matter.

Accordingly, applicants respectfully request that the obviousness rejection of claims 1, 13, 14, 33, 40, 41, 56, 63, and 64 over the cited combination be withdrawn. Allowance of these claims is also respectfully requested.

Obviousness Rejection No. 5

Claims 1, 10, 33, 37, 56, and 60 have been rejected over the combinations recited in the above-discussed Obviousness Rejection Nos. 1-3, and further as evidenced by Price. Accordingly to the Patent Office, in addition to the asserted disclosures presented above with reference to Obviousness Rejection Nos. 1-3, Price discloses a BAG retroviral vector. After careful consideration of the instant rejection and the Patent Office's asserted basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Applicants respectfully submit that even assuming *arguendo* that the Patent Office's characterization of the Price reference is correct, this reference does not cure

the deficiencies discussed hereinabove for the combination of Couture and Faustinella. The BAG vector has a complete 3' U3, and is similar to Couture in that expression of the gene of interest is directed by a fully functional LTR. This is in contrast to the presently claimed vectors, which subsequent to promoter conversion do not contain a complete 3' LTR. Applicants respectfully submit that Price does not provide the motivation to create a retroviral vector that is characterized by an partially deleted 3' U3 region, and thus the Patent Office has not presented a *prima facie* case of obviousness.

Accordingly, applicants respectfully request that the obviousness rejection of claims 1, 10, 33, 37, 56, and 60 over the cited combination be withdrawn. Allowance of these claims is also respectfully requested.

Obviousness Rejection No. 6

Claims 17, 20, 21, 26, 28, 43, 50-53, 66, and 73-76 have been rejected over the combinations recited in the above-discussed Obviousness Rejection Nos. 1-3, and further as evidenced by Longmore and Kay. Accordingly to the Patent Office, in addition to the asserted disclosures presented above with reference to Obviousness Rejection Nos. 1-3, the Patent Office asserts that Longmore and Kay disclose the use of retroviral vectors in animals. After careful consideration of the instant rejection and the Patent Office's asserted basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Applicants respectfully submit that even assuming *arguendo* that the Patent Office's characterization of the Longmore and Kay references is correct, these references do not cure the deficiencies discussed hereinabove for the combination of Couture and Faustinella. More particularly, the spleen focus-forming virus of Longmore and the modified LNCX vector of Kay both have a complete 3' U3. This is in contrast to the presently claimed vectors, which subsequent to promoter conversion direct transcription of the gene of interest through a promoter lacking a complete U3 sequence. As a result, Longmore and Kay do not cure the deficiencies of the Couture and Faustinella references discussed herein.

Accordingly, applicants respectfully request that the obviousness rejection of claims 17, 20, 21, 26, 28, 43, 50-53, 66, and 73-76 over the cited combination be withdrawn. Allowance of these claims is also respectfully requested.

Conclusions

In light of the above amendments and remarks, applicants respectfully submit that claims 1, 5, 7, 9-26, 28, 29, and 31-78 are in condition for allowance at this time, and respectfully solicit a Notice of Allowance to that effect.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: 09/02/2004 By: _____

Arles A. Taylor, Jr.
Registration No. 39,395

1406/194 AAT/CPP

Customer No: 25297